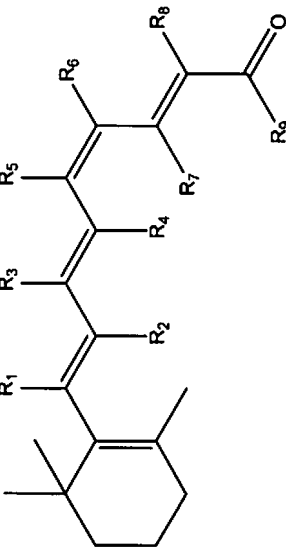
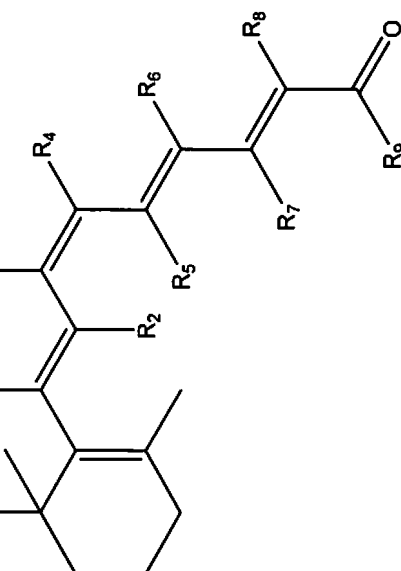


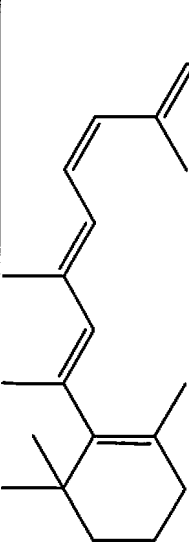
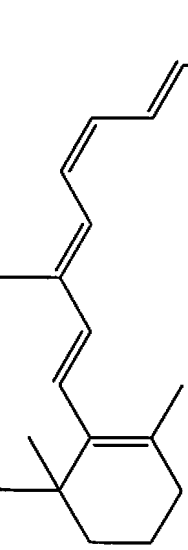
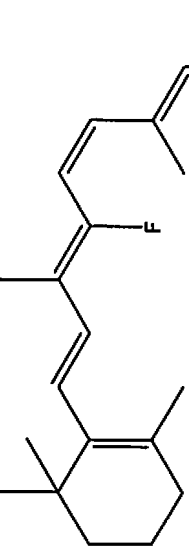
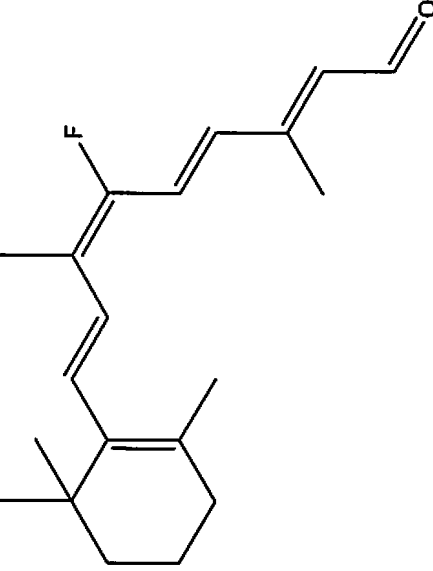
REMARKS/ARGUMENTS

The specification has been amended to more explicitly express the inherent inclusion of derivatives of 9-*cis*-retinal in paragraph [0045] on pages 8-9. Original formula III has been renamed formula “IIIa” and formula “IIIb,” where the latter corresponds to derivatives of 9-*cis*-retinal with a 9-*cis*-retinoid backbone. This amendment has been introduced to better correspond to the disclosure at the beginning of paragraph [0045].

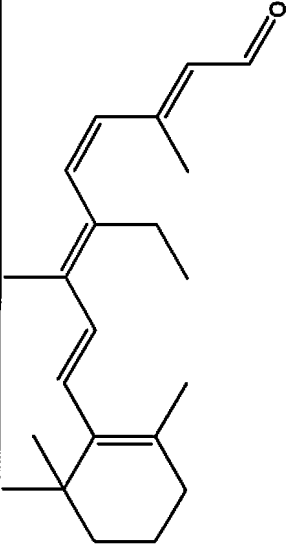
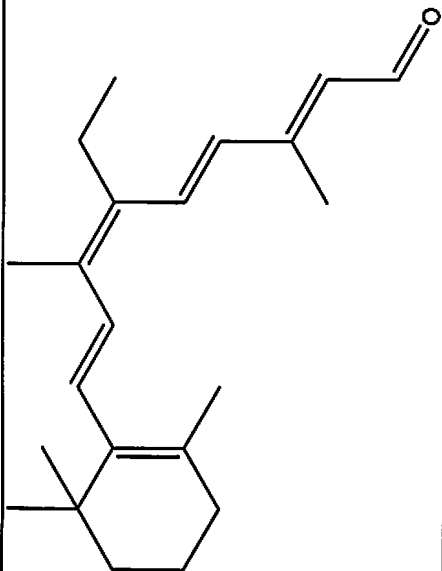
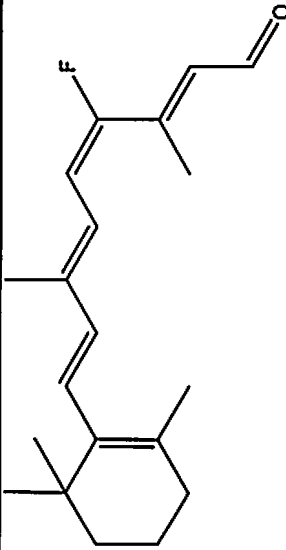
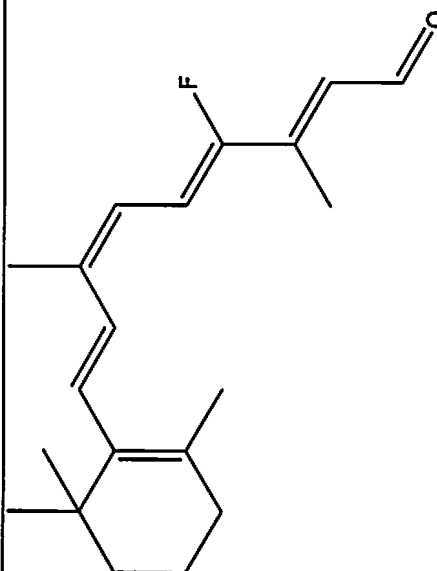
Additional support for the introduction of formula IIIb is provided by the following Table A, which shows each of formulas IIIa and IIIb with the structures of all the exemplary compounds listed at the end of paragraph [0045].

Table A. Exemplary Compounds of Formulas IIIa and IIIb

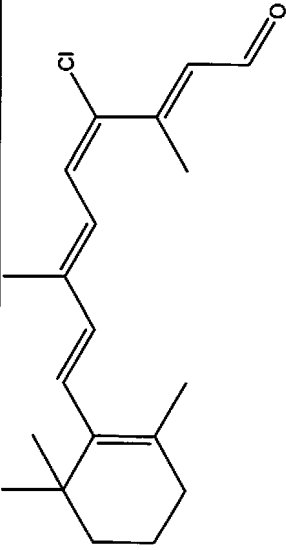
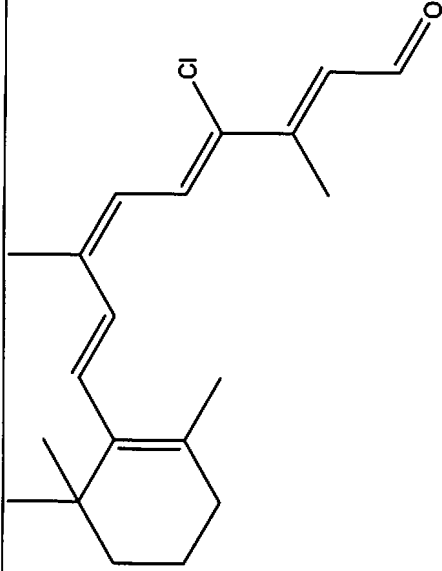
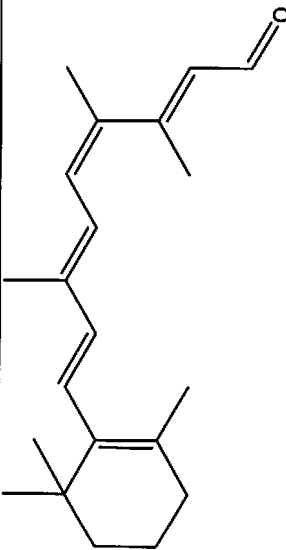
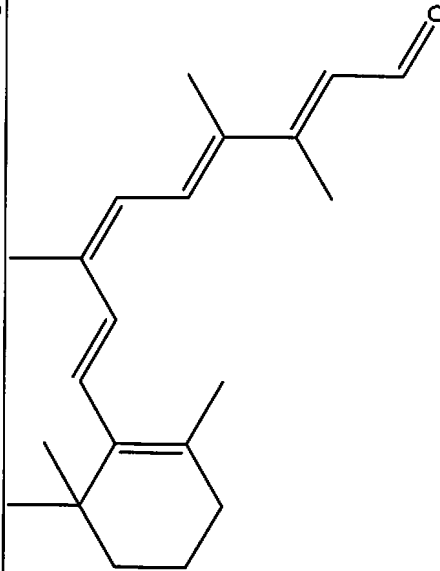
Name of Exemplary compound in paragraph [0045]	Structure of "derivative of an 11- <i>cis</i> -retinal" compound Formula IIIa:	Name of Exemplary compound in paragraph [0045]	Structure of "derivative of a 9- <i>cis</i> -retinal" compound Formula IIIb:	Support in paragraph [0045] for formulas IIIa and IIIb
9-ethyl-11- <i>cis</i> -retinal				R3=ethyl R7=methyl

7-methyl-11- <i>cis</i> -retinal				R1=methyl/ R3=methyl/ R7=methyl/
13-desmethyl-11- <i>cis</i> -retinal				R3=methyl/
11- <i>cis</i> -10-F-retinal		9- <i>cis</i> -10-F-retinal		R3=methyl/ R4=fluoro R7=methyl/

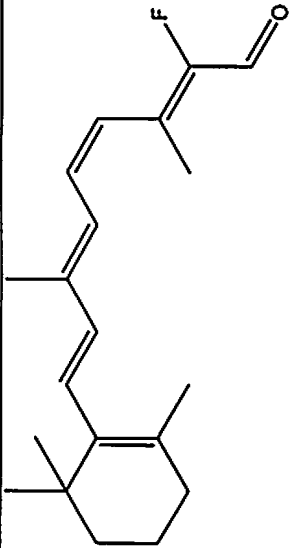
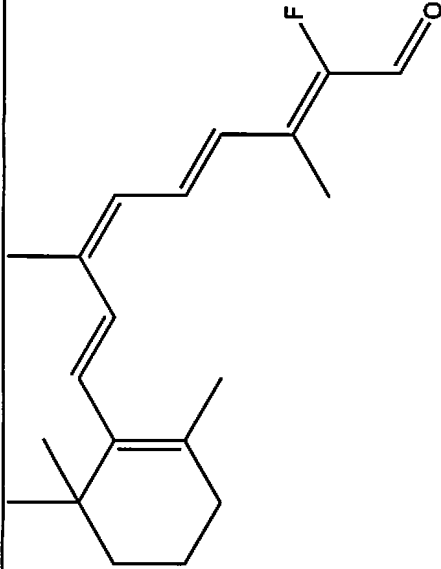
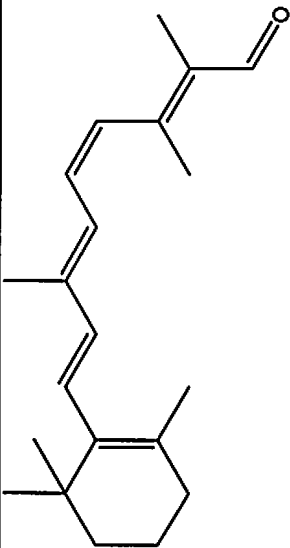
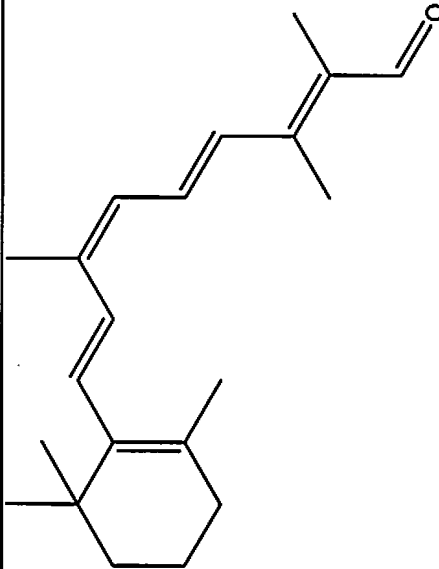
11- <i>cis</i> -10-Cl-retinal		9- <i>cis</i> -10-Cl-retinal		R3=methyl R4=chloro R7=methyl
11- <i>cis</i> -10-methyl-retinal		9- <i>cis</i> -10-methyl-retinal		R3=methyl R4=methyl R7=methyl

11- <i>cis</i> -10-ethyl-retinal		9- <i>cis</i> -10-ethyl-retinal		R3=methyl R4=ethyl R7=methyl
11- <i>cis</i> -12-F-retinal		9- <i>cis</i> -12-F-retinal		R3=methyl R6=fluoro R7=methyl

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11- <i>cis</i> -12-Cl-retinal		9- <i>cis</i> -12-Cl-retinal		R3=methyl R6=chloro R7=methyl
11- <i>cis</i> -12-methyl-retinal		9- <i>cis</i> -12-methyl-retinal		R3=methyl R6=methyl R7=methyl

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11- <i>cis</i> -14-F-retinal		9- <i>cis</i> -14-F-retinal		R3=methyl R7=methyl R8=fluoro
11- <i>cis</i> -14-methyl-retinal		9- <i>cis</i> -14-methyl-retinal		R3=methyl R7=methyl R8=methyl

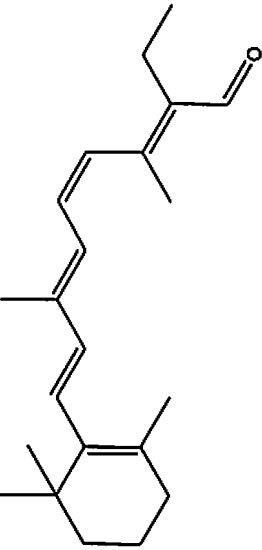
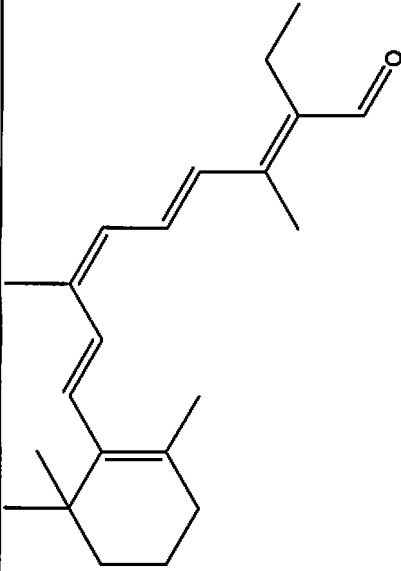
11- <i>cis</i> -14-ethyl-retinal		9- <i>cis</i> -14-ethyl-retinal		R3=methyl R7=methyl R8=ethyl
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Table A shows that all of the exemplary compounds at the end of paragraph [0031] are within the scope of formulas IIIa and IIIb. Additionally, the last 10 (ten) rows of Table A show retinal derivatives that have the same modifications *except for* the position of the *cis* bond, which is at either the 11- or 9- position as disclosed in paragraph [0031]. Accordingly, no new matter has been presented, and entry of the amendments to the specification is respectfully requested.

Paragraph [0031] has also been amended to correct two typographical errors.

Claims 16-18, 35-37, and 49-51 have been canceled in favor of new Claims 52-71. Support for the new claims is provided at least by the set of previous claims as indicated in the following table.

New Claim	Previous Claim
52-54 and 63	16
55-62	17, 18, 35-37, and 49-51
64-71	17, 18, 35-37, and 49-51

New Claim 52 is further supported by the instant specification as filed, especially with respect to “synthetic retinoid” and “derivative of 9-*cis*-retinal” (see for example page 7, paragraph [0027] of the application as filed). Additional support for Claim 52 is found on pages 12-13, paragraphs [0041] and [0042]; page 16, paragraph [0055]; page 17, paragraph [0057]; in Example 1, starting on page 18 of the specification as filed; and paragraph [0080] in the Example. For example, these passages disclose the use of an *in vitro* cell-based model or *in vivo* animal model to identify synthetic retinoids that induce folding and stabilization of the human P23H mutant opsin protein.

Additional information regarding knowledge in the art regarding transgenic mouse models expressing the human P23H mutant opsin protein is provided by Olsson et al. (1992, Neuron 9:815-830). A copy of Olsson et al. is enclosed herewith.

Support for new independent Claim 53 is provided by the revisions to pages 8-9 as explained above.

No new matter has been introduced, and entry of the revised claims is respectfully requested.

Examiner Interviews

Applicants thank Examiner Huang for the courtesy of an in-person interview on April 14, 2010 with the undersigned. During the interview, the claims in the Supplemental Response filed April 6, 2010 were discussed. Applicants thank Examiner Huang for her careful review of the application as filed and the disclosure relating to Formula III on pages 12-13 (paragraph [0045]) as well as an understanding of Applicants' view of that paragraph and the omission of a "9-*cis*-retinoid" backbone corresponding to the "11-*cis*-retinoid" backbone that is present in the paragraph.

Applicants thank Examiner Huang for the courtesy of a telephonic interview on April 22, 2010 with the undersigned. Examiner Huang conveyed the Office's view regarding the omission of a "9-*cis*-retinoid" backbone as described above and how insertion of a "formula IIIb" could be made to introduce a "9-*cis*-retinoid" backbone without raising "new matter" issues. Examiner Huang further indicated that any claim that contains "formula IIIb" was to include all the R₁ to R₉ possibilities recited on pages 8-9, paragraph [0031]. The undersigned indicated a disagreement with this position.

Examiner Huang also indicated that the introduction of a formula for a "9-*cis*-retinoid" backbone should be limited to paragraph [0031] at the present time because other counterpart places in the specification with the same issue had not been fully reviewed.

Information Disclosure Statement (IDS)

The Action mailed November 15, 2009 indicates that the IDS filed September 23, 2009 was not accompanied by a copy of each of the 13 cited documents.

Applicants have reviewed the Image File Wrapper (IFW) for the instant application at the Office's website using "public PAIR" and point out that the IFW shows 13 "NPL" documents entered on September 23, 2009 with the submitted IDS.

Applicants respectfully submit that no further copies of the documents are necessary and that they should be considered and formally made of record in the instant application.

Claim Objections

The Action mailed November 15, 2009 indicates that Claims 19 and 35 did not include the proper claim identifiers. Applicants thank the Office for noting the minor clerical errors in those claim identifiers.

Because the claims at issue have been canceled in favor of the newly presented claims, Applicants believe that this issue is moot and that no substitute copy of the claims filed July 27, 2009 *with correct identifiers* is required. However, Applicants are prepared to submit a substitute copy if so required.

Reconsideration of the objections is respectfully requested.

Election/Restriction Requirement

Applicants acknowledge the indication in the Action mailed November 15, 2009 that there is no current election of species requirement for the pending claims. So there is no current requirement for election of a specific compound or between oral and local administration.

Accordingly, Applicants withdraw their previous voluntary shift in elected species from 11-cis-7-ring retinal (elected via the response filed February 8, 2008) to the compound encompassed by previous Claim 20, which was canceled with the Supplemental Response filed April 6, 2010.

Alleged Rejection Under 35 U.S.C. § 112, first paragraph

Claims 16-20, 35-37, and 49-51 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants

have carefully reviewed the statement of this rejection and respectfully traverse because no *prima facie* case of “new matter” is present with respect to these claims.

But because the claims at issue have been canceled in favor of the newly presented claims, Applicants believe that this issue is moot in light of the different claim language now being used.

So no *prima facie* case of “new matter” or an inadequate written description remains, and this rejection may be properly withdrawn.

Alleged Rejections Under 35 U.S.C. § 112, second paragraph

Claims 16-20, 35-37, and 49-51 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants have carefully reviewed the statement of this rejection and respectfully traverse.

However, and because the claims at issue have been canceled in favor of the newly presented claims, Applicants believe that this issue is moot in light of the different claim language now being used.

In the event that there remains an issue with the recitation of “a derivative of 9-*cis*-retinal” as present in Claim 51, Applicants respectfully point out that while the phrase may be broad, it is not indefinite. For example, the nature and structure of the synthetic retinoid includes a 9-*cis*-retinoid backbone that is “capable of inducing the *in vivo* folding and stabilization of a P23H mutant opsin protein to form visual pigment after intraocular injection into an eye of a transgenic mouse expressing the human P23H mutant opsin protein....”

Additionally, 9-*cis*-retinal *per se* **cannot** be within the scope of Claim 52 because it is not within the plain language of “a derivative of a 9-*cis*-retinal....” This is a necessary conclusion because “a derivative of” a molecule cannot be the same molecule without any derivatization.

In light of the foregoing, Applicants respectfully submit that no case of indefiniteness is present and that this rejection may be properly withdrawn.

Alleged Rejections Under 35 U.S.C. § 103

Claims 16-19, 35-37 and 49-51 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chapple et al. (ANCR, 3(1):12-13, 2003). Applicants have carefully reviewed the statement of the rejection as well as the cited document and respectfully traverse because no *prima facie* case of obviousness is present.

Before addressing the statement of rejection and the cited document, Applicants point out that the Office has failed to provide adequate evidence that Chapple et al. is cited as art under 35 U.S.C. § 102(b). The guidance set forth at MPEP 2128.02 and in the case decisions cited therein indicate the need for an affidavit to establish factors such as normal time frame and practice for publication and delivery for access by the public. But the copy of the email from publisher Rachael Hansford fails to demonstrate a date of public availability of Chapple et al. The statement by Ms. Hansford does not indicate first-hand knowledge of the publication process in the time period of March and April, 2003. It isn't even clear that Ms. Hansford was the Publisher at that time. Additionally, satisfaction of the requirements of 35 U.S.C. § 102(b) cannot be based upon Ms. Hansford's guess. Accordingly, Applicants understand Chapple et al. as cited under 35 U.S.C. § 102(a) until adequate evidence to the contrary is provided.

And even though the rejected claims have been canceled, Applicants believe that a comparison of the cited document to the above-presented claims may be helpful. Applicants point out that Chapple et al. report the "addition of 9-*cis*-retinal to cultures expressing P23H mutant opsin improves the amount of opsin that reaches the plasma membrane whilst having no effect on K296E mutant opsin" (see page 13, left column, last paragraph, first sentence).

Applicants have explained above how the claims do not encompass administration of 9-*cis*-retinal. Moreover, Chapple et al. fail to teach or suggest that a derivative of 9-*cis*-retinal can be used to induce *in vivo* folding and stabilization of a P23H mutant opsin protein to form visual pigment as featured in the claims. Therefore, the skilled person would receive no guidance and no expectation of success from Chapple et al. to arrive at the claimed invention.

Accordingly, this cited document cannot form the basis of a rejection against the pending claims.

Claims 35-37 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chapple et al. (as cited above) in view of Lang (Adv. Drug Deliv. Rev. 16(1):39-43, 1995) and Geroski et al. (IOVS 41(5):961-964, 2000). Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully traverse because no *prima facie* case of obviousness is present.

Even though the rejected claims have been canceled, Applicants respectfully point out that the deficiencies of Chapple et al. have been explained above. The documents by Lang and Geroski et al., whether each is taken alone or in combination with the other, fail to teach or suggest a 9-*cis*-retinal derivative as featured in the claims. Accordingly, no combination of the three cited documents can lead a skilled person to the pending claims presented above. Therefore, these documents cannot form the basis of a rejection against the pending claims.

Conclusion

In light of the foregoing, Applicants respectfully submit that the claims are allowable and urge early indication to that effect. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at number below.

Respectfully submitted,

Date: June 7, 2010

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